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Original Article

Association between Bone Metabolism and the Severity of Chronic Heart Failure in Chinese Elderly Men and Women

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SUMMARY

Background: The role of bone metabolism markers for identifying the severity of chronic heart failure (CHF) in elderly adults had not been comprehensively investigated.
Methods: 335 elderly patients (mean age 83.98 years, women 36.72%) were divided into mild CHF (NYHA class I+II) group and severe CHF (NYHA class III+IV) group. We performed a binary logistic regression analysis to identify the independent association of bone metabolism markers with the severity of CHF. Besides, we used ROC curve to explore the predictability of bone metabolism markers on CHF severity.
Results: BMD levels of femoral neck in severe CHF group were significantly lower than that in mild CHF group with no gender difference. However, CTX-I, OC, PINP, ALP and PTH levels were significantly increased only in women with severe CHF. CTX-I (OR = 1.003, p = 0.008) was identified as an independent influencing factor positively associated with the severity of CHF in women after controlling for covariates. The predictability of CTX-I, OC, PINP and ALP for CHF severity was superior to NT-proBNP.
Conclusion: The association between bone metabolism and CHF severity varied by genders. Bone metabolism markers, especially the CTX-I, might be a possible risk marker associated with CHF severity independent of NT-proBNP in women.

1. Introduction

In China, approximately 70 million and 210 million people suffered from osteoporosis (OP) and osteopenia (OS), respectively.[1] Bone mineral density (BMD) measured by duel-energy X-ray dual-energy absorptiometry was the "gold parameter" for the diagnosis of OP and OS. However, repeat BMD was not advocated within 12 months as the changes did not generally attain significance within that time. Bone metabolism markers on the other hand showed significant change by 3-6 months. Chronic heart failure (CHF) is a critical health problem which ranked as the leading cause of hospitalization in China.[2] For that reason, the number of potential markers that could contribute to diagnosis and treatment of CHF patients was, almost exponentially, increasing over the recent years.

CHF as a chronic disorder associated with a myriad of metabolic disturbances, might unfavorably affect bone metabolism and predisposed to an exaggerated bone loss. Previous studies demonstrated the association of heart failure (HF) with the risk of future osteoporosis and related fractures, particularly in the hip area.[3–5] Low BMD appeared to be an independently predictor of significant coronary artery disease, which is the main cause of CHF.[6] Wu C, et al. reported that patients with severe HF displayed increased bone metabolism markers such as CTX-I and PTH.[7] The strength of a marker in CHF was its ability to guide the clinician in management as well as prognosis through multiple measurements during the clinical course.

In previous study[8] we had shown that BMD levels in elderly CHF patients were related to New York Heart Association (NYHA) classification. However, the role of bone metabolism markers for identifying severe CHF (NYHA class III+IV) had not been comprehensively investigated. Therefore, we attempted to investigate whether the assessment of bone metabolism could link to CHF severity in this study.

2. Materials and methods

2.1. Participants

Patients from January 2014 to December 2016 attending our hospital for evaluation of HF were included. We used patients' medical records rather than directly contacting them. The risk of this research was no more than the minimum risk. And the researchers had promised to protect the privacy of participants. Hence, according to the 39th provisions of Chinese law, The Ethical Review of Human Biomedical Research (2016), the Medical Ethics Committee of Zhejiang Hospital agreed to exempt the patients consent.

CHF patients were categorized into NYHA class I+II (mild CHF) group and NYHA class III+IV (severe CHF) group due to few par-

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ticipants being in NYHA class I (4.8%) and class IV (3.6%).

2.2. Inclusion and exclusion criteria

The inclusion criteria included: (1) age ≥ 60y; (2) meeting the criterion of European Society of Cardiology (ESC);[9] (3) being clinical stability and had taken BMD and bone metabolism markers measurements. The exclusion criteria mainly included metallic prosthesis/fixation at hip, renal insufficiency, advanced non-cardiac diseases or malignant tumor, connective tissue or musculoskeletal diseases, significant liver, thyroid, parathyroid gland, adrenal gland or pituitary diseases.

2.3. Bone status measurement

A Dual-Energy X-ray Absorptiometry (GE Lunar-I DXA, GE Medical Systems, Madison, WI, USA) was used to measure BMD (g/cm^2) and T scores. The WHO defined individuals with a T-score between < -1 SD and -2.5 SD as having osteopenia and a T-score of -2.5 SD or below as having osteoporosis.[10]

2.4. Biochemical markers

C-terminal telopeptide of type I collagen (CTX-I), osteocalcin (OC) and N-terminal propeptide of type I collagen (PINP) were determined by the Immulite automated immunoassay systems (Diagnostic Products Corporation). Alkaline phosphatase (ALP), parathyroid hormone (PTH), 25 hydroxy vitamin D [25(OH)D], calcium (Ca) and phosphorus were assessed using the Unicel DxI 800 immunoassay system (Beckman Coulter, Inc., Brea, California, USA). N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was measured by the electrochemical luminescence using Roche Cobas E601 analyzer (Switzerland).

2.5. Statistical analysis

Evaluation of normality was performed with Shapiro-Wilk test. Continuous variables were described as mean ± standard deviation or median (25th, 75th percentile). Comparisons between two groups were done by Student t test or Mann-Whitney U-test. Categorical variables were presented as n (%) and compared by Chi-square analysis. Clinically significant variables, and variables found to be statistically significant in Table 2 and Table 3 ($p < 0.1$) were then tested by a binary logistic regression analysis with forward LR subset selection to search for the independent factors associated with the severity of CHF. Receiver operator characteristic (ROC) curve analysis was performed to identify the predictability of bone metabolism markers on CHF severity. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA), $p < 0.05$ was considered statistically significant.

3. Results

3.1. Univariate analysis

The severe CHF (NYHA class III+IV) group had significantly higher NT-proBNP level, which is the marker of CHF severity. The difference confirmed the classification by NYHA classes.

Female CHF patients had significantly lower femoral neck (FN) BMD levels and higher CTX-I, OC and phosphorus levels than those of male patients (Table 1). FN BMD levels in severe CHF group were significantly lower than that in mild CHF (NYHA class I+II) group with no gender difference. However, CTX-I, OC, PINP, ALP and PTH levels were significantly increased only in women

Table 1
Comparison of variables by gender.

Variables	Men (n = 212)	Women (n = 123)	t/Z/χ^2 value	p value
Clinical data				
NYHA class			2.825	0.419
I	10 (4.717%)	6 (4.878%)		
II	142 (66.981%)	76 (61.789%)		
III	55 (25.943%)	34 (27.642%)		
IV	5 (2.358%)	7 (5.691%)		
Age (year)	86.000 (81.250, 90.000)	84.000 (79.000, 87.000)	-3.389	0.001
BMI (kg/m^2)	23.515 (21.480, 25.710)	23.440 (21.020, 25.300)	-0.789	0.430
Systolic pressure (mmHg)	134.730 ± 16.419	136.410 ± 18.056	-0.872	0.384
Diastolic pressure (mmHg)	70.600 ± 10.816	70.070 ± 10.404	0.446	0.656
Heart rate (bpm)	72.000 (64.000, 80.000)	72.000 (64.000, 77.000)	-0.566	0.572
Diabetes mellitus (%)	58 (27.358%)	33 (26.829%)	0.011	0.916
Smoking (%)	63 (29.717%)	3 (2.439%)	36.611	< 0.001
Alchohol (%)	39 (18.396%)	0 (0.000%)	25.609	< 0.001
BMD levels				
FN BMD (g/cm^2)	0.844 ± 0.157	0.711 ± 0.100	9.429	< 0.001
FN T-score	-1.100 (-1.800, -0.300)	-1.800 (-2.300, -1.200)	-6.099	< 0.001
Normal BMD	95 (44.800%)	21 (17.100%)		
Osteopenia	98 (46.200%)	77 (62.600%)	28.943	< 0.001
Osteoporosis	19 (9.000%)	25 (20.300%)		
Biochemical markers				
NT-proBNP (pg/mL)	238.750 (118.750, 776.83)	281.700 (127.700, 771.750)	-0.724	0.469
CTX-I (pg/mL)	349.000 (229.250, 490.575)	427.600 (286.200, 615.100)	-3.256	0.001
OC (ng/mL)	13.095 (9.815, 17.575)	16.000 (11.830, 21.210)	-4.076	< 0.001
PINP (ng/mL)	37.150 (25.930, 52.430)	38.950 (30.620, 54.280)	-1.198	0.231
ALP (U/L)	65.600 (52.300, 82.200)	63.750 (51.750, 80.400)	-0.514	0.607
PTH (pg/mL)	41.550 (29.475, 54.775)	38.300 (27.825, 53.350)	-0.721	0.471
25(OH)D (ng/mL)	15.150 (9.180, 21.440)	12.300 (8.950, 19.740)	-1.434	0.151
Ca (mmol/L)	2.225 (2.150, 2.310)	2.260 (2.170, 2.320)	-1.632	0.103
Phosphorus (mmol/L)	1.066 ± 0.186	1.204 ± 0.179	-6.003	< 0.001

ALP = alkaline phosphatase; BMD = bone mineral density; BMI = body mass index; Ca = calcium; CTX-I = C-terminal telopeptide of type I collagen; FN = femoral neck; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; OC = osteocalcin; 25(OH)D = 25 hydroxy vitamin D; PINP = N-terminal propeptide of type I collagen; PTH = parathyroid hormone.

with severe CHF (Table 2).

3.2. Binary logistic regression analysis

As the odds ratio (OR) indicated (Table 4), higher CTX-I (OR = 1.003, p = 0.008) and NT-proBNP (OR = 1.001, p = 0.041) levels were associated with higher odds of being in the severe status of CHF in women. Independent associations with CHF severity in men, were noted for osteopenia (OR = 3.333, p = 0.014), NT-proBNP (OR = 1.001, p = 0.002) and antiplatelet (OR = 0.300, p = 0.009).

3.3. ROC analysis

The area under the curve (AUC) for CTX-I, OC, PINP and ALP

Table 2
Differences of BMD and bone metabolism between mild and severe CHF group.

Variables	Men (n = 212)				Women (n = 123)			
	NYHA I + II (n = 152)	NYHA III + IV (n = 60)	t/Z/χ^2 value	p value	NYHA I + II (n = 82)	NYHA III + IV (n = 41)	t/Z/χ^2 value	p value
Clinical data								
Age (year)	85.000 (81.000, 89.000)	87.000 (82.250, 90.000)	-1.195	0.232	83.000 (79.000, 86.000)	85.000 (79.500, 88.000)	-1.510	0.131
BMI (kg/m^2)	23.724 ± 3.245	23.472 ± 3.706	0.490	0.625	23.545 (21.088, 25.588)	22.680 (20.400, 24.500)	-1.293	0.196
Systolic pressure (mmHg)	134.500 (122.000, 145.000)	132.500 (125.000, 146.750)	-0.011	0.991	136.320 ± 17.761	136.610 ± 18.855	-0.084	0.933
Diastolic pressure (mmHg)	69.950 ± 10.640	72.250 ± 11.170	-1.395	0.164	70.410 ± 10.359	69.370 ± 10.587	0.525	0.600
Heart rate (bpm)	71.000 (64.000, 80.000)	75.000 (65.000, 83.250)	-1.410	0.158	70.000 (64.000, 76.000)	76.000 (64.500, 80.000)	-1.731	0.083
Diabetes mellitus (%)	48 (31.600%)	10 (16.700%)	4.814	0.028	22 (26.800%)	11 (26.800%)	< 0.001	> 0.050
Smoking (%)	44 (28.9%)	19 (31.7%)	0.152	0.696	2 (2.4%)	1 (2.4%)	< 0.001	> 0.050
Alchohol (%)	30 (19.7%)	9 (15.0%)	0.643	0.423	0	0	-	-
BMD levels								
FN BMD (g/cm^2)	0.859 ± 0.159	0.806 ± 0.146	2.222	0.027	0.730 ± 0.095	0.673 ± 0.099	3.091	0.002
FN T-score	-0.900 (-1.800, -0.200)	-1.400 (-2.075, -0.425)	-2.235	0.025	-1.601 ± 0.776	-2.088 ± 0.780	3.274	0.001
Normal BMD	77 (50.700%)	18 (30.000%)	7.433	0.024	17 (20.700%)	4 (9.800%)	6.011	0.050
Osteopenia	63 (41.400%)	35 (58.300%)			53 (64.600%)	24 (58.500%)		
Osteoporosis	12 (7.900%)	7 (11.700%)			12 (14.600%)	13 (31.700%)		
Biochemical markers								
NT-proBNP (pg/mL)	206.350 (108.400, 393.670)	711.600 (213.050, 1719.750)	-3.627	< 0.001	248.300 (100.150, 467.800)	525.000 (204.400, 1878.000)	-2.482	0.013
CTX-I (pg/mL)	355.800 (236.900, 502.400)	322.150 (207.700, 450.600)	-1.138	0.255	391.850 (268.175, 548.275)	523.600 (372.900, 721.200)	-2.457	0.014
OC (ng/mL)	13.195 (10.205, 17.458)	12.645 (8.400, 19.250)	-0.666	0.505	15.720 (11.065, 19.895)	18.800 (13.665, 26.760)	-2.243	0.025
PINP (ng/mL)	36.920 (25.930, 51.480)	37.750 (25.810, 57.050)	-0.138	0.890	36.900 (28.250, 46.900)	44.430 (34.650, 78.230)	-2.540	0.011
ALP (U/L)	64.550 (50.800, 79.875)	69.700 (56.200, 84.400)	-1.804	0.071	64.010 ± 17.416	74.600 ± 29.455	-2.098	0.041
PTH (pg/mL)	42.500 (30.850, 54.950)	37.700 (26.500, 55.950)	-0.741	0.459	36.850 (26.300, 47.550)	45.600 (31.325, 75.950)	-2.706	0.007
25(OH)D (ng/mL)	15.000 (9.010, 21.020)	16.950 (10.100, 26.790)	-1.347	0.178	14.190 (8.790, 19.360)	11.990 (8.960, 20.350)	-0.166	0.868
Ca (mmol/L)	2.236 ± 0.112	2.219 ± 0.132	0.886	0.377	2.249 ± 0.096	2.253 ± 0.124	-0.185	0.854
Phosphorus (mmol/L)	1.077 ± 0.192	1.047 ± 0.177	0.982	0.327	1.196 ± 0.159	1.217 ± 0.211	-0.589	0.557

CHF = chronic heart failure.

Table 3
Cardiac medication use in CHF patients.

Variables	Men (n = 212)				Women (n=123)			
	NYHA I + II (n = 152)	NYHA III + IV (n = 60)	χ^2 value	p value	NYHA I + II (n = 82)	NYHA III + IV (n = 41)	χ^2 value	p value
Antiplatelet	117 (77.000%)	35 (58.300%)	7.366	0.007	60 (73.200%)	20 (48.800%)	7.151	0.007
Statin	108 (71.100%)	32 (53.300%)	6.022	0.014	53 (64.600%)	20 (48.800%)	2.848	0.092
ARB	78 (51.300%)	25 (41.700%)	1.603	0.205	46 (56.100%)	17 (41.500%)	2.343	0.126
CCB	70 (46.100%)	20 (33.300%)	2.849	0.091	43 (52.400%)	16 (39.000%)	1.971	0.160
β-receptor blockers	56 (36.800%)	20 (33.300%)	0.230	0.631	16 (19.500%)	13 (31.700%)	2.256	0.133
Spironolactone	5 (3.300%)	7 (11.700%)	4.194	0.041	2 (2.400%)	10 (24.400%)	12.570	< 0.001
α-glucosidase inhibitors	30 (19.700%)	7 (11.700%)	1.945	0.163	7 (8.500%)	7 (17.100%)	1.219	0.270
Nitrates	28 (18.400%)	10 (16.700%)	0.090	0.764	16 (19.500%)	3 (7.300%)	3.112	0.078
Insulin secretagogues	26 (17.100%)	4 (6.700%)	3.859	0.049	12 (14.600%)	5 (12.200%)	0.137	0.712
Biguanides	12 (7.900%)	1 (1.700%)	2.899	0.089	6 (7.300%)	2 (4.900%)	0.267	0.605

ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

were 0.757 (p = 0.002), 0.706 (p = 0.011), 0.704 (p = 0.012) and 0.697 (p = 0.016) respectively, which were superior to NT-proBNP (AUC = 0.687, p = 0.021) (Table 5) (Figure 1).

3.4. Medication treatment

In female patients prescribed with insulin secretagogues, FN BMD level was higher, however CTX-I, OC and PINP levels were lower (Table 6). Female patients taking ARB (CTX-I and PINP) and biguanides (OC and PINP) also showed lower levels of bone metabolism markers (Table 6). Male patients on therapy with insulin secretagogues (0.928 ± 0.200 vs. 0.830 ± 0.145, p = 0.014) and biguanides (0.959 ± 0.163 vs. 0.836 ± 0.154, p = 0.006) had higher FN BMD levels (data not shown).

4. Discussion

Elevated CTX-I, OC, PINP, ALP and PTH levels were presented in women with severe CHF (NYHA class III+IV) indicating increased bone metabolism with the progression in the clinical stage of CHF. Of various bone metabolism markers, the major determinants of CHF severity in women were NT-proBNP and CTX-I. However, the role of CTX-I in identifying CHF severity and in guiding treatment had not been determined. CHF shared many same risk factors with osteoporosis, such as older age, reduced physical performance, smoking, renal dysfunction and liver insufficiency. Higher CTX-I level indicated increased osteoclast activity and bone resorption. And in the view of Wu C, et al.,[7] the detected marker (CTX-I) showed biochemical evidence of increased bone resorption in patients with severe HF. Thus CTX-I might be used as a marker to predict CHF severity and an indicator for drug selection. This study reinforced the need for a better understanding of the potential causes and consequences of increased bone metabolism in CHF patients.

In clinical practice, BNP and NT-proBNP have been widely recommended as markers to define the diagnosis and prognosis in HF patients.[9,11,12] Elderly patients often have elevated NT-proBNP levels, due to the high prevalence of heart diseases.[13] And a clear evidence indicated that NT-proBNP was circulating in severe HF patients.[14] Bone metabolism can be easily and non-invasively assessed by the measurement of serum or urinary bone related markers. The development of markers of bone metabolism had provided an important tool in the clinical and pre-clinical assessment of bone active interventions,[15] and provided information that was complementary to BMD.

PTH is an important regulator of bone metabolism. Some studies showed that PTH level elevated as NYHA class increased,[16] and it was positively correlated with NT-proBNP level in HF patients.[17] Similarly, in our study PTH level was significantly elevated in women with CHF. Although increased PTH level in HF could be caused by various factors such as the activation of RAA system, chronic hyperaldosteronism, and the use of loop diuretics,[18] exact mechanisms still remained unknown.

Theoretically, the multiple disease pathologies, the numerous medications, the sedentary lifestyle, and the low BMD levels of severe CHF patients might all have contributed to the reduced bone metabolism. Moreover, CHF itself might adversely affect bone metabolism and induce a severe bone loss.[19] Medications used to

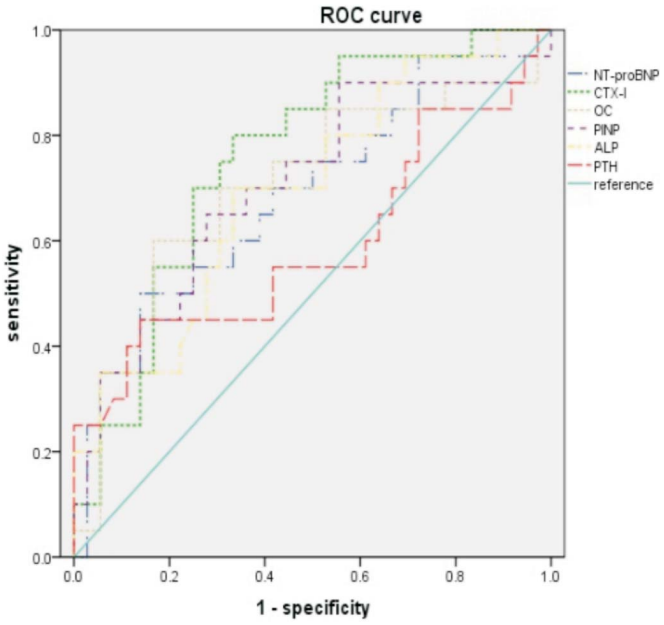

Figure 1. ROC curve for NT-proBNP, CTX-I, OC, PINP, ALP and PTH as a screening test for the severity of CHF in women.

Table 4
Binary logistic regression analysis for the severity of CHF.

Variables	Men (n = 212)		Women (n = 123)	
	OR (95% CI)	p value	OR (95% CI)	p value
Osteoporosis	3.839 (0.907, 16.247)	0.068	-	-
Osteopenia	3.333 (1.279, 8.688)	0.014	-	-
Normal BMD	-	-	-	-
NT-proBNP	1.001 (1.000, 1.001)	0.002	1.001 (1.000, 1.002)	0.041
CTX-I	-	-	1.003 (1.001, 1.006)	0.008
Antiplatelet	0.300 (0.122, 0.736)	0.009	-	-

CI = confidence interval; OR = odds ratio.

Table 5
Analysis of diagnostic tests on the severity of CHF in women.

Variables	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	p value
NT-proBNP (pg/mL)	518.250	0.500	0.861	0.667	0.756	0.687 (0.538, 0.837)	0.021
CTX-I (pg/mL)	474.950	0.800	0.667	0.571	0.857	0.757 (0.628, 0.886)	0.002
OC (ng/mL)	20.245	0.600	0.833	0.667	0.789	0.706 (0.553, 0.858)	0.011
PINP (ng/mL)	43.290	0.650	0.722	0.565	0.788	0.704 (0.555, 0.854)	0.012
ALP (U/L)	66.950	0.700	0.667	0.538	0.800	0.697 (0.553, 0.840)	0.016
PTH (pg/mL)	52.800	0.450	0.861	0.643	0.738	0.592 (0.422, 0.763)	0.255

AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value.

Table 6
Influence of medication on BMD and bone metabolism in women with CHF.

	FN BMD (g/cm^2)	FN T-score	CTX-I (pg/mL)	OC (ng/mL)	PINP (ng/mL)	ALP (U/L)	PTH (pg/mL)
ARB use							
Yes	0.723 ± 0.110	-1.671 ± 0.895	392.200 (241.100, 523.600)	15.930 (10.500, 20.650)	36.900 (28.090, 44.470)	64.400 (52.750, 80.725)	36.450 (27.350, 43.625)
No	0.699 ± 0.088	-1.860 ± 0.699	498.750 (340.975, 687.450)	17.055 (13.703, 22.113)	45.850 (33.270, 66.010)	63.250 (49.500, 80.150)	46.300 (29.325, 56.375)
t/Z value	1.293	1.306	-2.171	-1.290	-2.752	-0.268	-1.870
p value	0.199	0.194	0.030	0.197	0.006	0.789	0.062
Spironolactone use							
Yes	0.662 ± 0.127	-2.167 ± 0.988	503.900 (216.050, 899.075)	17.305 (13.658, 27.493)	54.020 (36.380, 88.920)	77.900 (45.100, 96.900)	56.600 (41.100, 86.200)
No	0.717 ± 0.096	-1.720 ± 0.778	422.700 (290.100, 605.900)	15.930 (11.640, 21.130)	38.450 (29.800, 49.010)	63.600 (52.550, 80.050)	37.400 (27.150, 50.450)
t/Z value	-1.823	-1.839	-0.571	-0.899	-2.021	-0.555	-2.856
p value	0.071	0.068	0.568	0.369	0.043	0.579	0.004
Insulin secretagogues use							
Yes	0.765 ± 0.111	-1.306 ± 0.907	290.300 (139.100, 514.000)	11.100 (9.120, 15.575)	29.900 (21.870, 36.240)	54.200 (43.000, 76.450)	38.100 (24.650, 46.400)
No	0.703 ± 0.096	-1.837 ± 0.770	444.650 (313.050, 632.125)	17.320 (13.563, 22.478)	43.240 (32.660, 59.640)	65.200 (52.800, 82.000)	38.400 (30.000, 53.800)
t/Z value	2.448	2.574	-2.242	-3.437	-3.308	-1.656	-1.121
p value	0.016	0.011	0.025	0.001	0.001	0.098	0.262
Biguanides use							
Yes	0.734 ± 0.131	-1.575 ± 1.095	341.250 (128.100, 661.100)	11.300 (9.045, 17.570)	27.690 (21.170, 36.040)	48.600 (42.175, 71.450)	41.000 (15.850, 54.725)
No	0.710 ± 0.098	-1.777 ± 0.788	433.400 (290.100, 615.100)	16.170 (12.990, 21.490)	40.030 (32.450, 56.060)	64.550 (52.650, 80.575)	38.150 (28.850, 53.350)
t/Z value	0.649	0.681	-1.036	-2.128	-2.172	-1.736	-0.421
p value	0.517	0.497	0.300	0.033	0.030	0.083	0.674

treat CHF in this study, including ARB, insulin secretagogues and biguanides might protect against osteoporosis. In contrast, spironolactone might make osteoporosis worse.

It is important to note that clinical value of individual markers within the single time points for both diagnosis and outcome prediction in CHF is limited. Hence, the future of marker application in CHF lied in the multimarker panel strategy, which would include specific combination of markers that reflected different pathophysiological processes underlying CHF. On the basis of these observations, we hypothesized that bone metabolism markers might be the risk indicators for defining the progression of CHF. It is promising to use CTX-I as an indicator for guiding CHF management.

Several limitations were noted. First, the retrospective study design could only describe association. Second, the findings were based on medical records, which might decrease the reliability and generalizability of our results. Third, the sample size of patients with NYHA class I and IV was rather small. Fourth, several key clinical covariates including CAD, other CVD and CKD (or eGFR) were not included in this study due to the limitation of the original medical records. Last, it would be interesting to enroll non-CHF subjects as control group in the future study, which might reveal the correlations in more detail.

5. Conclusions

In conclusion, this study provided evidence for the association between increased bone metabolism and CHF severity. Our data suggested that bone metabolism markers could be used as the complementary indicators in addition to the NYHA classification and NT-proBNP in identifying severe CHF patients (NYHA class III+IV). CTX-I might be a reference marker for the risk stratification of CHF patients especially in women. Some medications used to treat CHF could have impacts on bone metabolism. Careful screening for bone metabolism markers and appropriate medication usage were important considerations in CHF patients.

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Conflicts of interest

The authors report no any conflicts of interest in this work.

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